PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Cyclopentanophenanthrene Derivatives and process for the Production thereof

We, SYNTEX S.A., Apartado Postal 2679, Mexico City, Mexico, a Corporation of Mexico, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to cyclopentanophenanthrene compounds and to a process for the production thereof.

The present invention relates especially to novel 1,2 - dimethyl estrone and estradiol derivatives and to a novel process for the production thereof. The novel compounds of the present invention are estrogenic hormones generally suitable for the treatment of prostate cancers i.e. they show weak estrogenic activity together with anti - androgenic activity. They also lower blood cholesterol levels.

In our U.K. Specification 853,291, there is disclosed the production of the novel 2α - methyl testosterone. In accordance with the present invention it has been discovered that this compound upon treatment with an oxidizing agent capable of oxidizing the 17 - hydroxyl group to a keto group yields the novel intermediate and androgenic hormone 2α - methyl - Δ^4 - androstene - 3,17 - dione. Further this last mentioned compound upon treatment with approximately 2 mols of bromine gives the novel intermediate 2α - methyl - 2,6 - dibromo - Δ^4 - androstene - 3,17 - dione which yields the novel 2α - methyl - $\Delta^{1,4,6}$ - androstatriene - 3,17 - dione upon treatment with a dehydrohalogenating agent. Finally the $\Delta^{1,4,6}$ - triene derivative is treated with a lower fatty acid anhydride to rearrange and form the 3 - lower fatty acid ester of 1,2 - dimethyl - 6 - dehydro - estrone and the last mentioned compound saponified.

From this last mentioned compound there may be prepared other novel 1,2 - dimethyl estrone and estradiol derivatives, viz. 1,2 - dimethyl - 6 - dehydro - estradiol, 1,2 - dimethyl - 17α - ethinyl - 6 - dehydro - estradiol, 1,2 - dimethyl - estrone, 1,2 - dimethyl-estradiol and 1,2 - dimethyl - 17α - ethinyl-estradiol. From these compounds by conventional means there may also be prepared their novel esters with hydrocarbon carboxylic acids of less than 12 carbon atoms.

The novel 1,2 - dimethyl estrone and estradiol derivatives of the present invention may therefore be represented by the following formulae:

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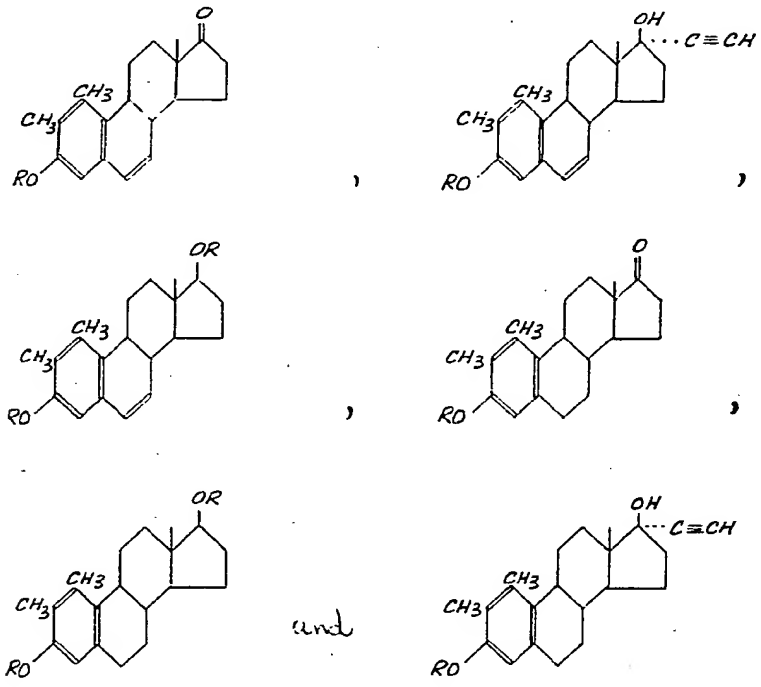
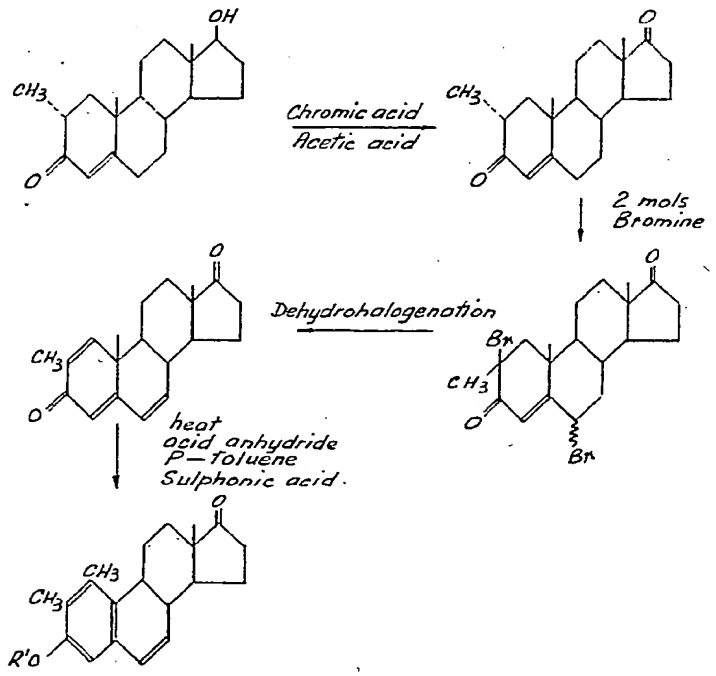


In the above formulae R represents an acyl group derived from a hydrocarbon carboxylic acid of less than 12 carbon atoms such as acetic, propionic, caproic, benzoic, cyclopentylpropionic, or phenylpropionic, or R represents hydrogen.

A part of the process of the present invention may be exemplified by the following scheme:

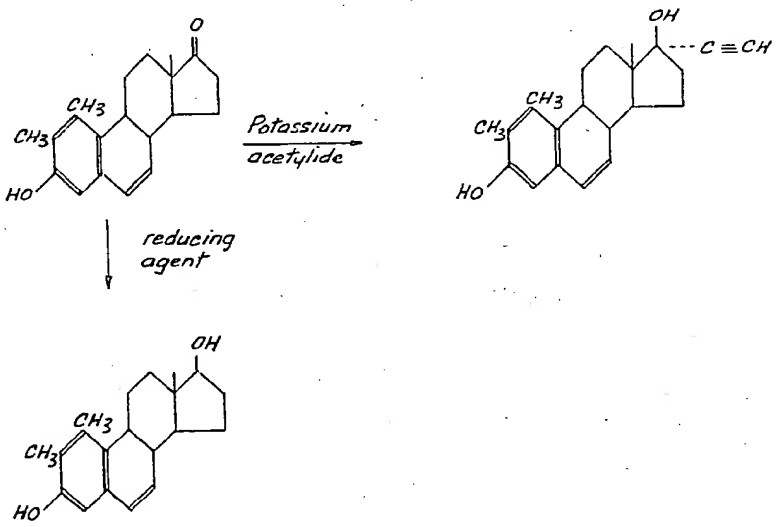


In the above scheme R^1 represents a lower fatty acyl group, e.g. acetyl or propionyl depending on the particular acid anhydride of the last step indicated, or upon conventional saponification, hydrogen.

In practising the process above outlined the 2α - methyl testosterone (2α - methyl - Δ^4 - androsten - 17β - ol - 3 - one) is preferably dissolved in glacial acetic acid and the solution cooled below room temperature. Chromic acid (slightly over 1 equivalent) in acetic acid is then added slowly with stirring and while maintaining the reaction mixture below room temperature. The reaction mixture is then allowed to stand for a period of the order of 2 hours at room temperature, poured into ice water and the precipitate of 2α - methyl - Δ^4 - androstene - 3,17 - dione is collected and purified e.g. by crystallization from an alcoholic solvent. For the next step of the process outlined above the product of the first step is suspended in an organic solvent such as ether to which a catalytic amount of hydrogen bromide in acetic acid is added. To this suspension there is slowly added slightly over 2 mols of bromine in acetic acid. The resulting clear solution is allowed to stand for one hour and then concentrated under reduced pressure until crystallization of the 2,6 - dibromo - 2α - methyl - Δ^4 - androstene - 3,17 - dione has taken place. The crystals are then filtered and washed with a small amount of ether.

As indicated in the scheme the 2,6 - dibromo compound upon treatment with a dehydrohalogenating agent gives as a product 2 - methyl - $\Delta^{1,4,6}$ - androstatriene - 3,17 - dione. As a suitable dehydrohalogenating agent a tertiary amine, such as collidine under reflux is used. Preferably the dibromo compound is refluxed with the collidine for a short period of the order of 1 hour and then cooled. The product is separated from the collidine hydrobromide and purified to give 2 - methyl - $\Delta^{1,4,6}$ - androstatriene - 3,17 - dione. This product upon treatment with a lower fatty acid anhydride, e.g. acetic or propionic, and *p* - toluenesulphonic acid, e.g. by heating on a steam bath for a few hours, rearranges to form the corresponding 3 - lower fatty acid ester of 1,2 - dimethyl - 6 - dehydro - estrone. Conventional saponification of these compounds e.g. with methanolic alkali metal hydroxide or with an acid, gives the free 1,2 - dimethyl - 6 - dehydro - estrone. From the free compound by conventional acylation procedures e.g. by reaction with corresponding acid anhydrides or acyl halides there are then prepared esters of hydrocarbon carboxylic acids of less than 12 carbon atoms such as those previously set forth.

1,2 - dimethyl - 6 - dehydro - estrone is utilized as an intermediate for the production of 1,2 - dimethyl - 6 - dehydro - derivatives such as 1,2 - dimethyl - 6 - dehydro - estradiol and 1,2 - dimethyl - 17α - ethinyl - 6 - dehydro - estradiol in accordance with the following scheme:

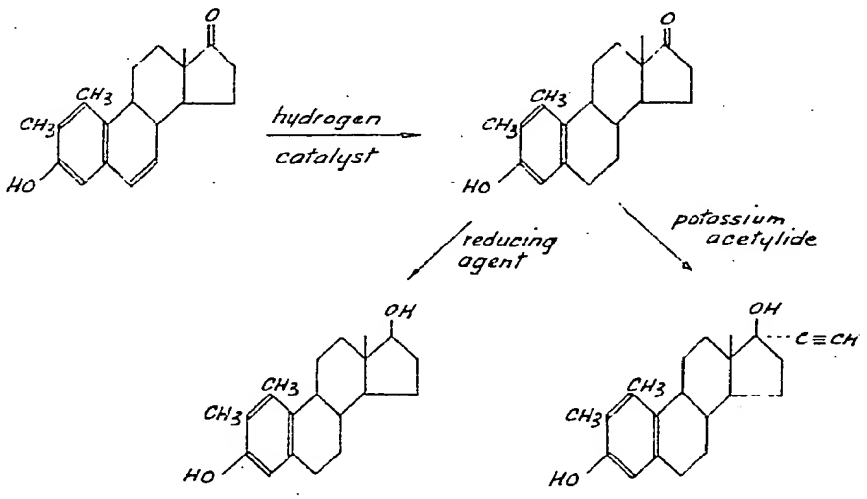


To prepare the ethinyl estradiol derivative as indicated above the 17 - keto compound is reacted with potassium acetylide prepared *in situ*. Thus the 1,2 - dimethyl - 6 - dehydro - estrone may be dissolved in an organic solvent, such as benzene, and added to a solution of potassium metal in a tertiary alcohol such as *t* - butyl alcohol. Acetylene is then passed into the reaction mixture for a prolonged period of time of the order of 2 days. Neutralization with acid and removal of the organic solvents by steam distillation results in a precipitate of the product which is then purified e.g. by crystallization.

For the production of the estradiol derivative the estrone compound is treated with a

reducing agent, preferably an alkali metal hydride such as sodium borohydride or lithium aluminium hydride in alcohol - water solution.

Similarly with prior hydrogenation the intermediate 1,2 - dimethyl - 6 - dehydro - estrone can be utilised for the preparation of 1,2 - dimethyl - estrone, 1,2 - dimethyl - estradiol and 1,2 - dimethyl - 17α - ethinyl - estradiol in accordance with the following scheme:



As indicated above hydrogenation in the presence of a hydrogenation catalyst, preferably palladium or platinum, until 1 mol of hydrogen is taken up gives the corresponding 1,2 - dimethyl - estrone. Reaction with a reducing agent or with potassium acetylide as previously described in connection with the 6 - dehydro compounds gives the corresponding 1,2 - dimethyl estradiol and 17α - estradiol derivatives.

It may be noted further that all of the non-tertiary alcohol groups in both the 6 - dehydro and corresponding 6 - saturated compounds previously described may be conventionally esterified as with acid anhydride or acyl halides to give either mono or diesters as previously indicated.

The following specific examples serve to illustrate but are not intended to limit the present invention.

EXAMPLE I

A solution of 710 mg. (1.1 equivalents) of chromic acid in 15 cc. of 80% acetic acid was added dropwise to a stirred solution of 3.0 g. of 2α - methyl - Δ^4 - androsten - 17β - ol - 3 - one in 30 cc. of glacial acetic acid, while the temperature was maintained below 20°C. After 2 hours standing at room temperature the mixture was poured into ice water and the precipitate was collected, well washed with water and crystallized from methanol, thus giving 2α - methyl - Δ^4 - androsten - 3,17 - dione.

A suspension of 2.5 g. of the above compound in 50 cc. of ether containing 3 drops of a saturated solution of hydrogen bromide in acetic acid, was slowly treated with a solution of 2.8 g. (2.1 mols) of bromine in 30 cc. of acetic acid. The resulting clear solution was kept standing for 1 hour and then concentrated under reduced pressure until crystallization. The 2,6 - dibromo - 2α - methyl - Δ^4 - androsten - 3,17 - dione produced was filtered and washed with a little ether.

3.0 g. of the 2,6 - dibromo derivative was refluxed for 1 hour with 10cc. of collidine and then cooled. The precipitate of collidine hydrobromide was filtered and well washed with ether and the solution was washed with dilute hydrochloric acid, with sodium bicarbonate and water, dried and evaporated to dryness. Chromatographic treatment of the residue with 100 g. of alumina afforded the pure 2 - methyl - $\Delta^{1,4,6}$ - androstatrien - 3,17 - dione.

A mixture of 1.0 g. of 2 - methyl - $\Delta^{1,4,6}$ - androstatriene - 3,17 - dione, 40 cc. of acetic anhydride and 300 mg. of *p* - toluenesulphonic acid was heated on the steam bath under anhydrous conditions for 4 hours. The cooled mixture was poured into 500 cc. of water and kept standing overnight at room temperature. The precipitate was filtered, well washed with water, dried and crystallized from acetone - hexane, thus yielding the acetate of 1,2 - dimethyl - 6 - dehydro - estrone.

0.5 g. of the above acetate in 30 cc. of methanol was treated under nitrogen with 0.2 g. of potassium hydroxide in 2 cc. of water. The mixture was kept for 1 hour at room temperature and then acidified with acetic acid and concentrated to one third of its volume. Dilution with water and filtration of the precipitate yielded the free 1,2 - dimethyl - 6 - dehydro - estrone which was crystallized from acetone - hexane. This compound was only

about 1/1000 as estrogenic as estrone in the mouse uterus essay but shows antiandrogenic activity in chicks fed with testosterone.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3 - propionate, 3 - benzoate, 3 - cyclopentylpropionate and the 3 - phenylpropionate.

EXAMPLE II

A solution of 0.3 g. of 1,2 - dimethyl - 6 - dehydro - estrone in 20 cc. of methanol was treated with a solution of 0.2 g. of sodium borohydride in 3 cc. of water. After keeping the mixture for 3 hours at room temperature, it was treated with a few drops of acetic acid and diluted with salt water. The precipitate was collected, washed with water and crystallized from acetone - hexane, thus producing 1,2 - dimethyl - 6 - dehydro - estradiol.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3,17 - dipropionate, 3,17 - dibenzoate, 3,17 - dicyclopentylpropionate and the 3,17 - diphenylpropionate.

A solution of 0.5 g. of 1,2 - dimethyl - 6 - dehydro - estrone in 20 cc. of anhydrous benzene was added under an atmosphere of nitrogen to a cooled solution of 0.5 g. of potassium metal in 25 cc. of *t* - butyl alcohol, which had been prepared under an atmosphere of nitrogen. The stream of nitrogen was then substituted by a stream of dried and purified acetylene and the operation was continued for 40 hours. The solution was poured into 100 cc. of dilute hydrochloric acid, the organic solvents were removed by steam distillation and after cooling the precipitate was collected. Crystallization from chloroform - methanol afforded 1,2 - dimethyl - 17α - ethinyl - 6 - dehydro - estradiol.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3 - propionate, 3 - benzoate, 3 - cyclopentylpropionate and the 3 - phenylpropionate.

0.5 g. of 1,2 - dimethyl - 6 - dehydro - estrone in 25 cc. of ethyl acetate was stirred under an atmosphere of hydrogen, at atmospheric pressure and room temperature, in the presence of 100 mg. of a 10% palladium on charcoal catalyst which had been previously reduced in 10 cc. of ethyl acetate. After the equivalent of 1 mol of hydrogen had been absorbed, the solution was filtered and evaporated to dryness. Crystallization from acetone - hexane yielded 1,2 - dimethyl - estrone.

This compound was only about 1/1000 as estrogenic as estrone in the mouse uterus essay but shows anti - androgenic activity in chicks fed with testosterone. Further when fed to rats by the oral route it partially counteracts the injection of testosterone.

Conventional reaction of this compound with acid anhydride and/or chlorides gave the corresponding 3 - propionate, 3 - benzoate, 3 - cyclopentylpropionate and the 3 - phenylpropionate.

0.3 g. of 1,2 - dimethyl - estrone in 20 cc. of methanol was treated with a solution of 0.2 g. of sodium borohydride in 3 cc. of water. After 3 hours at room temperature the mixture was treated with a few drops of acetic acid and diluted with salt water. The precipitate was filtered, washed with water and crystallized from acetone - hexane giving 1,2 - dimethyl - estradiol. This compound was 1/200 as estrogenic as estrone in the mouse uterus essay.

A solution of 0.5 g. of 1,2 - dimethyl - estrone in 20 cc. of anhydrous benzene was added under an atmosphere of nitrogen to a cooled solution of 0.5 g. of potassium metal in 25 cc. of *t* - butyl alcohol which had also been prepared under an atmosphere of nitrogen. The stream of nitrogen was then substituted by a stream of dried and purified acetylene and the operation was continued for 40 hours. The solution was poured into 100 cc. of dilute hydrochloric acid, the organic solvents were removed by steam distillation and the precipitate was filtered from the cooled mixture. Crystallization from chloroform - methanol produced 1,2 - dimethyl - 17α - ethinyl - estradiol.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3 - propionate, 3 - benzoate, 3 - cyclopentylpropionate and the 3 - phenylpropionate.

WHAT WE CLAIM IS:—

1. In a process for the production of a 1,2 - dimethyl - 6 - dehydro - estrone compound, 1,2 - dimethyl - 6 - dehydro - estradiol compound, 1,2 - dimethyl - estrone compound or 1,2 - dimethyl - estradiol compound, the steps comprising treating 2α - methyl - Δ^4 - androsten - 17β - ol - 3 - one with an oxidizing agent to form 2α - methyl - Δ^4 - androstene - 3,17 - dione, treating the dione with approximately 2 mols of bromine to form the corresponding 2,6 - dibromo compound, treating the dibromo compound with a dehydrohalogenating agent to form the corresponding $\Delta^{1,4,6}$ - triene derivative, treating the $\Delta^{1,4,6}$ - triene derivative with a lower fatty acid anhydride to rearrange and form the 3 - lower fatty acid ester of 1,2 - dimethyl - 6 - dehydro - estrone and saponifying the last mentioned compound.

2. Process according to claim 1, wherein the oxidizing agent is chromic acid in acetic acid.

3. Process according to claim 1 or claim 2, wherein the dehydrohalogenating agent is a tertiary amine, e.g. collidine.

4. Process according to any preceding claim, wherein the triene is rearranged with acetic acid and *p* - toluenesulphonic acid.

5. A process according to claim 1 substantially as herein described and exemplified.

6. Product obtained by the process claimed in any preceding claim.

7. 1,2 - Dimethyl - 6 - dehydro - estrone or an ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

8. 1,2 - Dimethyl - 6 - dehydroestradiol or a diester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

9. 1,2 - Dimethyl - estrone or an ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

10. 1,2 - Dimethyl - estradiol or a diester thereof with a hydrocarbon carboxylic acid thereof of less than 12 carbon atoms.

11. 1,2 - Dimethyl - 6 - dehydro - 17α - ethinyl - estradiol or a 3 - ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

12. 1,2 - Dimethyl - 17α - ethinyl - estradiol or a 3 - ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

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